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[Intervention Review]

Interventions for intermittent exotropia

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ABSTRACT

Background

The clinical management of intermittent exotropia has been discussed extensively in the literature, yet there remains a lack of clarity regarding indications for intervention, the most effective form of treatment and whether or not there is an optimal time in the evolution of the disease at which any treatment should be carried out.

Objectives

The objective of this review was to analyse the effects of various surgical and non-surgical treatments in randomised trials of participants with intermittent exotropia, and to report intervention criteria and determine the significance of factors such as age with respect to outcome.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library,* Issue 4, 2012), MEDLINE (January 1966 to May 2012), EMBASE (January 1980 to May 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to May 2012), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 4 May 2012. We are no longer searching the UK Clinical Trials Gateway (UKCTG) for this review. We manually searched the British Orthoptic Journal up to 2002, and the proceedings of the European Strabismological Association (ESA), International Strabismological Association (ISA) and American Academy of Paediatric Ophthalmology and Strabismus meeting (AAPOS) up to 2001. We contacted researchers who are active in the field for information about further published or unpublished studies.

Selection criteria

We included randomised controlled trials of any surgical or non-surgical treatment for intermittent exotropia.

Data collection and analysis

Each review author independently assessed study abstracts identified from the electronic and manual searches. Author analysis was then compared and full papers for appropriate studies were obtained.

Main results

We found one randomised trial that was eligible for inclusion. This trial showed that unilateral surgery was more effective than bilateral surgery for correcting the basic type of intermittent exotropia.

Authors' conclusions

The available literature consists mainly of retrospective case reviews, which are difficult to reliably interpret and analyse. The one randomised trial included found unilateral surgery more effective than bilateral surgery for basic intermittent exotropia. However, across all identified studies, measures of severity and thus criteria for intervention are poorly validated, and there appear to be no reliable natural history data. There is therefore a pressing need for improved measures of severity, a better understanding of the natural history and carefully planned clinical trials of treatment to improve the evidence base for the management of this condition.

PLAIN LANGUAGE SUMMARY

Treatment for a type of childhood strabismus where one or both eyes intermittently turn outwards

Strabismus is a condition in which the eyes are not normally aligned, that is one eye looks straight ahead whilst the other eye turns inwards, outwards, up or down. Most cases of childhood onset strabismus are present constantly, but some types are intermittent that is only present sometimes. In intermittent exotropia (X(T)) an eye intermittently turns outwards (exotropia), typically more when looking into the distance, when tired or day-dreaming. When the child focuses on something close, the eye usually moves back to the centre. The eyes typically work together normally when the exotropia is controlled. When the exotropia occurs, the image from one eye is usually switched off or 'suppressed'. Treatment for X(T) may be sought to improve the appearance of misalignment or if there is concern that it is affecting the ability of the eyes to work together. Treatment typically consists of surgery on the muscles around the eye, either on the outside muscle of both eyes or on the inside and outside muscle of one eye. Exercises to strengthen the muscles may sometimes be used; sometimes patching or glasses for short or near sightedness can be tried. There is currently not a clear understanding of which treatments work most effectively and at what point any treatment should be given. We searched for studies where participants with X(T) had been randomised to receive treatment. The aim was to understand which treatments are most effective at correcting the exotropia without causing any harm. The one study included in this review was conducted by a single surgeon in the USA and compared surgery on one eye to surgery on both eyes in 36 children with the basic type of X(T). Success was defined as no exotropia (or other strabismus) one year following surgery. The study found that surgery on one eye was more effective (82% success) than surgery on both eyes (52% success). There are many studies of X(T) in the current literature but the methods used make it difficult to reliably interpret the results. Furthermore, there is a worrying lack of evidence regarding the natural history of X(T) and poor validation of measures of severity. There is a clear need for further randomised studies to provide more reliable evidence for the management of this condition.

BACKGROUND

Description of the condition

Epidemiology

Ocular misalignment (strabismus) develops in approximately 5% of developmentally normal children (Graham 1974). Of these approximately 25% present with an outward turning ocular deviation or exotropia (Jenkins 1992). The most common type of childhood onset exotropia is intermittent exotropia (X(T)) (Mohney 2003), with a reported incidence rate of 32.1/100,000 in children under 19 years of age in the United States of America (Govindan 2004) and occurring more frequently in Asian populations (Chia 2007; Matsuo 2005), in latitudes with greater sunlight (Jenkins 1992) and in females (Nusz 2005).

The term 'intermittent exotropia' may be used to describe any non-constant exotropia but it is typically (and throughout this review) used to describe the type of exodeviation that is present predominantly at distance fixation with or without deviation at near fixation. Pseudonyms include distance exotropia, divergence excess exotropia, periodic exotropia and exotropia of inattention. Intermittent exotropia is sometimes subdivided into 'basic' and 'distance' subtypes but clinical characteristics are very similar for these subtypes of X(T) and, as investigation and management are also essentially the same (Cooper 1977), they are considered together in this review and jointly referred to as 'intermittent exotropia' or X(T).

Natural history

The natural history of X(T) is not well documented. An early study by von Noorden (von Noorden 1966) is quoted (von Noorden 2002) as finding 75% of patients progressing over an average of three years, but the original report is unavailable. Conversely, a contemporary report by Hiles (Hiles 1968) reported six year follow-up angle data on X(T) patients who 'for various reasons' were not operated upon and found that 81% showed no change. Findings vary among more recent studies also, some reporting that most cases improve over time (Rutstein 2003), some that most remain stable (Chia 2005; Kii 1992; Romanchuk 2006) and others that most will deteriorate (Nusz 2005). However, all these studies are retrospective reviews of participants who did not have surgery (or follow up until surgery was performed) and criteria for surgical intervention were not standardised, biasing results. Most current teaching texts describe X(T) as generally being progressive (Mitchell 2000; Santiago 1999; von Noorden 2002), but in the absence of rigorous studies the true natural history of X(T) remains uncertain. A multicentre, randomised controlled trial that aims to report natural history data is currently underway in the United States (http://ClinicalTrials.gov/show/NCT01032330). The completion date is 2015 and results will be included in updates of this review.

Presentation and diagnosis

Clinical characteristics

The onset of X(T) is thought to be in the first year of life (Costenbader 1950). The aetiology is unknown although various anatomical, innervational, sensory and genetic factors have been suggested (Burian 1971; Cooper 1977; Jampolsky 1962). The characteristic features of X(T) are unique: one eye deviates outward, typically when viewing a distant object, during periods of inattention, in bright sunlight or when the person is tired (Burian 1966). Closure of one eye in bright sunlight, sensitivity to sunlight (Campos 1992; Wang 1988; Wiggins 1990) and panoramic viewing (Cooper 1979; Costenbader 1950) are other common features of X(T). Diplopia (double vision) appears to be rarely noticed as suppression occurs when the deviation is manifest (Parks 1975; Pratt-Johnson 1969).

Normal use of the eyes together at near fixation (binocular single vision (BSV)) and normal near stereoacuity (three dimensional vision or depth perception) can usually be demonstrated when the exotropia is controlled (Holmes 2007; O'Neal 1995; Stathacopoulos 1993; Yildirim 2000). However, a proportion of people with X(T) demonstrate subnormal BSV and reduced near stereoacuity due to monofixation syndrome (23% Baker 1979; 31% Beneish 1994; 11.3% Yildirim 2000; and in another study, between 36% and 55% depending on the test used Hatt 2010a), a feature that is recognised to be part of the spectrum of the disease.

Visual acuity is typically normal in both eyes. A United States study reported amblyopia present only rarely (4.5%) and a normal distribution of refractive errors (Mohney 2003). Other studies report a higher prevalence of myopia in children with X(T) compared to the general population (Caltrider 1983). In Asian populations there is a preponderance of myopia (43%) in children with X(T) compared to children with esotropia (inward turning strabismus) (Chia 2007).

Intermittent exotropia may be associated with other eye movement anomalies, mainly overaction of the inferior oblique muscle (Mitchell 2000; Wilson 1989) and lateral incomitance (a decrease in amount of exodeviation on side gaze) (Clarke 1981; Moore 1969; Repka 1991; von Noorden 2002). The reported incidence of lateral incomitance varies (9% Repka 1991; 22% Moore 1969; 60% Clarke 1981) and, importantly, may be erroneously induced as an artifact of testing (Repka 1991). Systemic associations with X(T) include mental illness, with a recent study reporting a higher incidence of mental illnesses in patients with X(T) compared to patients with esotropia and compared to the general population (Mohney 2008).

Diagnostic tests

A diagnosis of X(T) is made using the cover test and by measuring the magnitude of exodeviation, typically using the prism cover test. These tests are performed with the individual fixing on an accommodative target at distance fixation and then at near fixation. The cover test shows an intermittent or constant exotropia either at distance fixation only or also at near fixation. Additional measurement of the exodeviation with the individual fixing on a far distance target has been recommended to uncover the maximum misalignment (Burian 1971b; Knapp 1960; Kushner 1998b).

Measurement of the exodeviation using the prism cover test at distance and near provides information regarding the degree of misalignment and subtype of X(T). The basic type of X(T) shows a similar angle of deviation at distance and near, and the distance type of X(T) shows a greater deviation at distance fixation. The distance type (or 'divergence excess') was originally described as an exodeviation measuring at least 10 prism dioptres greater at distance than near (Burian 1965). The distance type has been subdivided into 'simulated' (pseudo) or 'true' types based on the presence or absence of fusion (motor control of eye position) or focusing mechanisms at near: in the 'simulated' distance X(T) the near angle of deviation increases, either when fusion is disrupted (by occlusion of one eye) or focusing is relaxed (with plus lenses) (Cooper 1982; Kushner 1998; Walklate 1998) so that, under those

conditions, the deviation appears more like the basic type of X(T). In the 'true' type of distance X(T) the angle remains smaller at near despite manipulation of focusing and fusing mechanisms. When assessed in this way, 'true' distance X(T) appears to be relatively uncommon (Kushner 1998; Walklate 1998). Determining whether or not a patient has basic X(T), simulated distance X(T), or true distance X(T) is considered important prior to any surgery because different surgical approaches have been recommended depending on the subtype (Burian 1965; Hardesty 1978; Kushner 1998a; von Noorden 2002). However, some have suggested that surgery should be based on the distance deviation alone (Mitchell 2000; Stoller 1994).

Severity of X(T)

Determining the severity of X(T) relies principally on evaluating: 1) angle of exodeviation, 2) ability to control the exodeviation, and 3) stereoacuity (as an indicator of the quality of BSV). Traditionally, patients with a large angle of exodeviation, poor control or reduced stereoacuity, or a combination, are considered more severe. However, quantification of severity is poorly standardised.

1. Angle of deviation: there is no clearly defined threshold at which the angle of exodeviation is recognised as more severe. In addition, the angle cannot be considered in isolation from the ability to control, with a small but nearly constant exodeviation presenting a greater threat to binocularity than a large but well controlled exodeviation. There does not appear to be a strong correlation between angle of deviation and ability to control. Test-retest data on angle of deviaton were recently reported (Hatt 2012) and at distance were 3.4 prism dioptres for angles < 20 prism dioptres and 7.2 prim dioptres for angles > 20 prism dioptres. These data provide guidelines for evaluating change in angle over time. Data in children with esotropia have been reported (PEDIG 2008) but may not translate to children with X(T) as there may be greater variability in the underlying condition.

2. Control: recently developed control scales enable quantification of ability to control the exodeviation at a given point in time (Chia 2005; Haggerty 2004; Mohney 2006; Petrunak 2004; Stathacopoulos 1993). However considerable variation in control is now known to occur (Hatt 2007). Parental observations are often used and are incorporated into some control scales (Haggerty 2004; Stathacopoulos 1993). However these non-standardised observations will vary depending on how much time a parent spends with their child etc. Recently, the average of three measures of control during an examination has been shown to be superior to single or double (average of two) measures of control, as it more closely represents the patient's control over the whole day (Hatt 2011).

3. Stereoacuity: deterioration of near stereoacuity to below normal thresholds, or loss of near stereoacuity, is taken to be a sign of increasing severity, although this is rarely reported. A recent study by Holmes et al (Holmes 2011) reported infrequent deterioration of near stereoacuity in a cohort of children with X(T). More recently, distance stereoacuity testing has increasingly become part of clinical assessment, with deterioration in or loss of distance stereoacuity suggested as a sign of increased severity (O'Neal 1995; Stathacopoulos 1993; Yildirim 1999). Of note, distance stereoacuity may measure as either normal or subnormal in patients with X(T) depending on the test used (Holmes 2007). Children with X(T) seem to show greater test-retest variability than patients with constant strabismus (Adams 2008). It is important to remember that some patients with X(T) have reduced or no measurable stereoacuity at baseline due to monofixation syndrome.

Description of the intervention

As children with X(T) do not generally report symptoms such as asthenopia (frontal headaches and eyestrain) or diplopia, the aim of treatment is often to normalise or improve ocular alignment whilst maintaining or improving binocular functions and stereoacuity. For this majority of children with X(T) who are asymptomatic, criteria for intervention are poorly defined. Generally treatment may be offered if the physician or parents, or both, estimate the amount of time the eyes are misaligned (exotropic) to be equal to or greater than the amount of time they are aligned and working together. That is, exotropia present greater than or equal to 50% of waking hours (Santiago 1999; von Noorden 2002) is often used as a guideline and is based on concerns that in children extended periods of misalignment cause suppression to become established resulting in loss of BSV (Pratt-Johnson 1969). Intervention may also be instigated when the appearance of the exotropia is causing problems socially, or when there is a desire to avoid such social problems. Recent studies have explored the role of measuring health-related quality of life in children with X(T) to more formally measure these potential social and function concerns (Hatt 2010b). Treatment may also be indicated if or when there is evidence of loss of stereoacuity, but this appears to be extremely rare.

How the intervention might work

Treatment may be either surgical, non-surgical or a combination of both.

Surgical treatment

Surgery involves adjusting the position or length of the horizontally acting eye muscles. Surgery should result in a complete correction of the exotropia and restoration of normal binocular alignment at distance and near fixation. Most commonly one of the following procedures is undertaken.

1. Two muscle unilateral surgery: the medial rectus muscle (rotates the eye inwards) is strengthened and the lateral rectus muscle (rotates the eye outwards) is weakened.
2. Bilateral surgery: the lateral rectus muscle is weakened on both eyes.
3. One muscle unilateral surgery: one lateral rectus muscle is weakened.

The degree of muscle adjustment is usually tailored to the size of the strabismus although published surgical tables vary. It has been suggested that the effect of a given surgical dose may be influenced by factors such as magnitude of deviation preoperatively, the difference between distance and near deviation, and age at time of surgery (Scott 1975). A randomised trial by Kushner (Kushner 1998b) concluded that surgery should aim to correct the maximum horizontal deviation, elicited either at far distance or following a period of occlusion, rather than the initial distance measurement. Prism adaptation or vergence after-effect testing is considered by some to be useful in determining the target angle for surgery (Dadeya 2003; Ohtsuki 2001).

Surgical success rates often appear to be disappointing, with both undercorrection (Clarke 1981; Koo 2006; Richard 1983; Scott 1981) and overcorrection (Dunlap 1971; Edelman 1988; Ing 1999; Pratt-Johnson 1977) recognised as causes of surgical failure. Recurrence of X(T) postoperatively appears a more common cause of failure than overcorrection (Burke 1985) and may occur more frequently over longer periods of follow up (Ekdawi 2008; Maruo 2001). Surgical failure due to persistent overcorrection (inward turning deviation) may cause diplopia, loss of normal BSV, reduction in stereoacuity and development of amblyopia (lazy eye). Reports of this complication range from 1.5% (Beneish 1994) to 27% (Edelman 1988).

Some authors have suggested that successful alignment is more likely when there is an initial overcorrection of the deviation (Hardesty 1978; Keech 1990; Koo 2006; Raab 1969; Scott 1981) that should resolve in the first six weeks following surgery (Mitchell 2000). Others report that a planned initial overcorrection is of no benefit (Ing 1999; Maruo 2001; Pratt-Johnson 1977). The age at surgery is thought by some to influence success; some authorities advocate early intervention to avoid entrenched suppression and achieve an optimal result (Abroms 2001; Asjes-Tydeman 2006; Pratt-Johnson 1977; Pratt-Johnson 1994), others suggest that surgery should be delayed until the child is older (Edelman 1988; Richardson 2001; von Noorden 2002; Wickens 1984), and others have concluded that age at surgery makes no difference to the outcome (Beneish 1994; Folk 1956; Ing 1999; Richard 1983; Stoller 1994).

Non-surgical treatment

Non-surgical treatment aims to encourage use of the eyes together by eliminating suppression (making the brain aware of the visual input from both eyes simultaneously), aiding recognition of diplopia when the eyes are misaligned, and building fusional reserves (motor control of the eyes) in order to aid control of the exodeviation.

Non-surgical treatment may consist of the following.

1. Exercises may be used to improve control of the deviation, usually in older children (Cooper 1976; Freeman 1989; Goldrich 1980).
2. Part-time occlusion regimes (Flynn 1975; Freeman 1989; Spoor 1979; Suh 2006) may result in improved control of the deviation, although long-term success is unknown with some reports noting only a temporary benefit.
3. Minus lens therapy (Caltrider 1983; Rowe 2009; Watts 2005) can be used to induce convergence (inward turning) and therefore reduce the amount of exodeviation. This treatment may be difficult in children with X(T) who do not otherwise need to wear glasses. Concerns that minus lens therapy may cause or increase myopia (near sightedness) appear to be unfounded (Kushner 1999; Rutstein 1989).
4. Prisms may be used to correct or overcorrect the exodeviation but often large amounts of prism are required and compliance may be difficult (Hardesty 1978; Pratt-Johnson 1979; Ravault 1972).

Other less commonly used non-surgical treatments are:

1. botulinum toxin injection into the lateral recti, with varying success (Scott 1990; Spencer 1997); and
2. biofeedback, although this does not seem to have been adopted clinically (Goldrich 1982).

Surgery combined with non-surgical treatment

Using non-surgical treatment as adjunct to surgery, pre- or postoperatively, or both, has been advocated by some (Coffey 1992; France 1992; Veronneau-Troutman 1971). Presurgery, treatment to eliminate suppression and teach awareness of diplopia is thought to increase the likelihood of obtaining a cure.

Why it is important to do this review

At present there are many different approaches to the management of X(T) in large part due to a lack of certainty regarding the most effective treatment(s) and when any intervention should be carried out.

OBJECTIVES

The primary objective of this review was to determine the effectiveness of surgical and non-surgical treatment of X(T) in restoring ocular alignment and achieving or maintaining binocular single vision (BSV). The effect of factors such as age and subtype of X(T) were to be reported and if possible included in subgroup analyses.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials that compared management strategies in people with X(T).

Types of participants

Participants in the trials were people diagnosed with X(T) as described under 'Presentation and diagnosis'. The participants must have had evidence of exodeviation on cover test or prism cover test or other recognised method for measuring ocular alignment.

As there is often poor classification of X(T), and differing nomenclature, any study that did not clearly describe inclusion of basic or distance types of intermittent exotropia (X(T)) was excluded. Studies were also excluded if other types of exotropia were included and data on X(T) could not be extracted, and if participants had received prior treatment.

Types of interventions

The interventions included were as follows.

1. Surgical:
a. any type of unilateral surgery;
b. any type of bilateral surgery.

2. Non-surgical:
a. fusion or convergence exercises;
b. occlusion for anti-suppression;
c. optical - minus lens therapy, tinted lenses, prisms;
d. Botulinum toxin A injection.

We examined the following comparisons.

1. Any surgical intervention versus observation alone.
2. Any non-surgical intervention versus observation alone.
3. Surgical versus any non-surgical intervention.
4. Unilateral versus bilateral surgery.
5. Surgical with any non-surgical adjunct pre- or postoperatively, or both, versus surgical without non-surgical adjunct.
6. Unilateral versus unilateral (e.g. one muscle on one eye versus two muscles on one eye).
7. Bilateral versus bilateral (e.g. one muscle on each eye versus two muscles on one eye and one muscle on the other).
8. Early surgery versus late surgery.
9. Non-surgical versus non-surgical intervention.

Types of outcome measures

Primary outcomes

- Motor alignment at near and distance fixation using the simultaneous or alternate prism cover test, or both, or using the synoptophore
- Stereoacuity at near using any age-appropriate test

Secondary outcomes

- Stereoacuity at distance
- Motor fusion test at near or distance, or both

Studies with any period of post-treatment follow up were included but we planned to discuss the potential effects of different lengths of follow up when reporting the results.

Adverse events

- Overcorrection of the deviation lasting beyond the initial postoperative period with or without symptoms of diplopia
- Development of amblyopia coinciding with postoperative overcorrection
- Complications resulting from non-surgical intervention
- Intraoperative surgical complications

We categorised any record of the above adverse effects as severe (requiring further surgery or treatment) or minor (not requiring further intervention).

Quality of life measures

We included any measure of patient-reported or parent-reported health-related quality of life or patient satisfaction.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 4, part of *The Cochrane Library* www.thecochranelibrary.com (accessed 4 May 2012), MEDLINE, (January 1950 to May 2012), EMBASE (January 1980 to May 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to May 2012), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 4 May 2012. We are no longer searching the UK Clinical Trials Gateway (UKCTG) for this review.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), *m*RCT (Appendix 5), ClinicalTrials.gov (Appendix 6) and the ICTRP (Appendix 7).

Searching other resources

We searched the British Orthoptic Journal from 1970 to 2002 for reports of trials. We also searched the proceedings of the following conferences using the keywords exotropia, intermittent, and divergence excess:

- European Strabismological Association (ESA), 1975 to 1997 and 1999 to 2001;
- International Strabismological Association (ISA), 1994;
- American Academy of Paediatric Ophthalmology and Strabismus meeting (AAPOS) 1995 to 2001.

We searched the reference lists of relevant studies for information on further relevant studies.

Prior to the initial publication of this review in 2003, we contacted researchers (Paediatric Ophthalmology and Strabismus mailbase in USA and UK) active in the field for information about further published or unpublished studies.

Data collection and analysis

Selection of studies

Both review authors independently screened the titles and abstracts obtained by the searches to establish whether they met the criteria as defined in 'Criteria for including studies in this review'. We obtained full copies of definitely or potentially relevant studies.

Methods to be used in updates to the review

Since the first publication of this review we have altered the remit to include a broader definition of intermittent exotropia (X(T)). This is largely because when going through the original search results we identified an obvious overlap between distance and basic subtypes, to the extent that clinically they are often not distinguished from each other and are considered by many clinicians to be essentially the same condition.

We will assess all eligible trials that are identified in future updates of this review according to the following methods.

Data extraction and management

Trial data will be collected independently by the review authors using a data collection form. We will then check for errors before entering the data in to Review Manager (RevMan 2012).

Assessment of risk of bias in included studies

Study quality will be assessed according to the methods set out in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The following parameters will be assessed: sequence generation; allocation concealment; masking (blinding) of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; as well as any other sources of bias. For each parameter, for each included trial, we will describe the methods used by study authors to deal with potential bias. These findings will be summarised in the text

of the results and also in a risk of bias table. We will also indicate whether the methods employed resulted in a low risk of bias, a high risk of bias, or whether it was 'unclear' and we were unable to make a judgement either way. We will attempt to contact the study authors for parameters graded 'unclear'.

Studies where there is a high risk of bias on any parameter will be included and sensitivity analyses conducted to assess the summary effect on the exclusion of these studies.

Data synthesis

We will summarise data from studies collecting the same outcome measure with similar follow up. We will use odds ratios or risk ratios for dichotomous data and weighted mean difference for continuous data. We will check for heterogeneity. If no heterogeneity is evident, we will use a random-effects model unless there are fewer than three trials in a comparison, when we will use a fixed-effect model. If heterogeneity is present we will not pool results but will present a descriptive overview of results.

Sensitivity analysis

Sensitivity analysis will be conducted to assess the size and direction of the effect of excluding trials assessed as inadequate in terms of concealment of randomisation or those with missing data or of questionable eligibility.

RESULTS

Description of studies

Results of the search

The electronic searches retrieved a total of 986 titles and abstracts.

In light of the amended inclusion criteria, we re-analysed the two papers we excluded in the original published version of the review. Kushner 1998b was still ineligible and was excluded but Kushner 1998a met our inclusion criteria and has been included in the update of the review.

Updated searches

An update search in March 2006 identified 610 new reports of studies. We requested the full texts for a total of six studies but these were unavailable for two papers (Collur 1998; Rajavi 2001). We attempted to contact the authors for further information but these attempts have been unsuccessful, and therefore these studies are currently excluded. If further information becomes available this will be updated. Three studies required translation: Broniarczyk-loba; Lui 1999; and Zeng 2005. After translation it became apparent that they were not eligible and were therefore excluded. We excluded the final study Martin 1989 as it was a non-comparative study. For further details of excluded studies please see the 'Characteristics of excluded studies' table.

An update search in November 2008 yielded a further 263 reports of studies. The Trials Search Co-ordinator scanned the search results and removed any references which were not relevant to the scope of the review. Two authors independently reviewed the remaining references but did not find any relevant reports of trials.

An update search in May 2012 yielded a further 45 titles and abstracts, four trials from ClinicalTrials.gov, two trials from ISRCTN registration, and one trial from the Australian New Zealand Clinical Trials Registry (ANZCTR). Two authors independently reviewed the remaining references and identified one trial awaiting assessment (ISRCTN04267774) and four ongoing trials (ISRCTN44114892, IXT1 2012, IXT2 2012 and ACTRN12610001053011). The trial awaiting assessment (ISRCTN04267774) was completed in year 2003 but there was no published report yet. We contacted the trial investigator and did not receive any feedback. We did not identify any other completed studies that could be included.

Included studies

In the included study (Kushner 1998a) 36 patients with basic X(T) were randomised to two different surgical procedures: bilateral lateral rectus recession or unilateral lateral rectus recession with medial rectus resection. These groups were compared to each other and also to a non-randomised group of 68 patients with simulated distance exotropia who all underwent bilateral lateral recession surgery. The randomised comparison of those with basic X(T) was reported in this review.

Outcomes were assessed at least one year post surgery and recorded as either satisfactory or unsatisfactory. A satisfactory outcome was recorded if there was no tropia and between 10 dioptres exophoria and five dioptres esophoria at any distance on cover and prism cover testing. Any degree of tropia, phoria greater than that stated above (by implication) or any additional treatment was considered an unsatisfactory outcome. Stereoacuity was not reported pre- or postoperatively. The amount of surgery performed was standardised by using surgical formula tables.

Excluded studies

See 'Characteristics of excluded studies' table.

Risk of bias in included studies

Allocation

The methods used for sequence generation and group allocation were not described in the manuscript. We contacted the author for further details and clarified that a computer generated random sequence was created and a randomisation assignment was put in a series of sequentially numbered sealed envelopes, the contents of which were unknown until after surgery was scheduled and informed consent obtained.

Blinding

There was no masking of participants or outcome assessor. Outcomes were assessed by the surgeon who performed surgery.

Incomplete outcome data

Two participants (one from each randomised group) were lost to follow up and were therefore excluded from the outcome analysis. All other included participants had complete outcome data.

Selective reporting

The results section of the manuscript reported that 99 patients were operated on during the study enrolment period, some of whom were excluded because they were recruited for another study (Kushner 1998b). As it was unclear why or how participants were included in this study rather than the other study, and at what point participants were randomised, we contacted the author for further information. Dr Kushner clarified that 29 patients were

excluded from the Kushner 1998a study because, according to a predetermined protocol, if they were eligible for the other study (Kushner 1998b) they were automatically selected for recruitment to it. We determined that this did not constitute selective reporting and that there was therefore a low risk of bias for this parameter.

Other potential sources of bias

Final outcomes were measured 'at least one year' following surgery, which varied from 12 to 15 months. It was unclear whether the variability in follow-up time was the same for both randomised groups, but further contact with the author confirmed that the study follow-up time was the same (12 to 15 months) for both randomised groups.

Patients selected for recruitment to this study were those who did not fulfil the inclusion criteria for the other randomised study running concurrently (Kushner 1998b). Therefore the group who were eligible for inclusion in Kushner 1998a were those whose exodeviation did not increase after a patch or while looking outdoors, representing a subset of the entire basic X(T) population. This was not spelled out in the manuscript but has more implications for the generalisability of the results than for conclusions regarding treatment effect.

Effects of interventions

Nineteen of 36 participants (19/36) were allocated to symmetrical lateral rectus recessions; 17/36 to unilateral lateral rectus recession and medial rectus resection. The range of follow up was 12 to 15 months. The age at surgery and mean angle of distance deviation was comparable between the groups.

Satisfactory results:

bilateral surgery 10/19 (52%);
unilateral surgery 14/17 (82%).

Unsatisfactory results:

bilateral surgery 9/19 (48%), 2/19 (11%) overcorrected and 7/19 (37%) undercorrected;
unilateral surgery 3/17 (18%), 1/17 (6%) overcorrected and 2/17 (12%) undercorrected.
These results were found to be statistically significantly different between the two groups ($P < 0.02$; x^2 test) favouring unilateral surgery for a successful outcome.

DISCUSSION

The management of X(T) is unlike most other types of childhood onset strabismus as most individuals already possess binocular single vision (BSV). The current literature contains a large body of retrospective case reviews and prospective non-randomised studies which, while useful for describing certain aspects of the condition and its management, generally do not help establish reliable guidelines for intervention or enable interpretation of treatment effectiveness. We found one randomised trial eligible for inclusion in this review, and a summary of the main results and implications are presented below. For an overview of current practice and the evidence on which it is based, the reader is referred to the background section of this review.

Summary of main results

The included trial by Kushner 1998a studied the effects of two different surgical approaches for correcting the basic type of X(T). A higher proportion of satisfactory outcomes was reported with unilateral recess resect surgery compared to bilateral lateral rectus recession surgery. This finding is consistent with the concept that surgery on the medial and lateral rectus muscles of one eye is appropriate in strabismus where there is little or no near distance disparity.

Criteria for 'success' following surgery were limited to motor alignment and therefore it is not possible to comment on the effect of surgery on sensory function (stereoacuity). As discussed in earlier sections of this review, surgery can sometimes result in reduction in or loss of stereoacuity. Nevertheless, any manifest strabismus was considered an 'unsatisfactory' outcome and therefore it is unlikely that any patient was classified a success in the presence of loss of stereoacuity. Unsuccessful treatment of X(T) is due to either overcorrection, causing an esodeviation, or undercorrection, causing a residual exodeviation. In the trial by Kushner 1998a 'unsatisfactory' outcomes were more often due to undercorrection of the exodeviation than overcorrection. Some have suggested that a planned, temporary overcorrection in the initial postoperative period will reduce the possibility of undercorrection. However, the initial postoperative eye position was not reported in the included trial so it is unclear whether or not overcorrection played a role in those who were successfully aligned. There do not appear to be rigorous studies assessing the long-term effects of initial surgical overcorrection on postoperative alignment.

Overall completeness and applicability of evidence

The basic type of X(T) constitutes a reasonably well defined subgroup of X(T), but it remains unclear how findings from the included trial may or may not apply to other subgroups of X(T). If simultaneous surgery on the medial and lateral recti of one eye is indeed more effective where there is little or no difference between the near and distance angle of deviation (near-distance disparity), it may be expected that in true X(T) where the near-distance disparity persists (larger distance deviation) surgery to both lateral recti would be more effective than unilateral recess or resect surgery. However, we did not find any trials comparing surgical or non-surgical treatments for the true type of X(T). We also did not find any studies comparing treatments for simulated X(T) so it remains unclear whether or not simulated X(T) may be treated as basic X(T), or whether different surgical or non-surgical treatments may be more effective.

The included trial contributes improved evidence for the management of X(T), but there remain several major questions and areas in need of further research.

1. Which clinical measures should be used to define severity?

Possible measures include angle of deviation, stereoacuity at near or distance, control, motor fusion reserves, and health-related quality of life.

2. What is the natural history of X(T)?

It remains unclear what proportion of patients are likely to deteriorate, improve, remain stable over time, and whether

there are prognostic indicators of deterioration, improvement, or stability. Is the current classification of X(T) appropriate?

3. What are appropriate intervention criteria?

Popular options include reduction in or loss of stereoacuity (at near or distance), deteriorating fusional control, large angle of deviation, or a combination; but potential thresholds remain poorly defined and current recommendations are not well validated.

4. Which criteria should be used to define 'success' following treatment?

Various criteria are used in the current literature: i) motor alignment only (e.g. within 10 prism dioptres of orthotropia), ii) motor alignment with stereoacuity, or iii) motor alignment with stereoacuity and other motor and sensory capabilities such as awareness of diplopia when tropic and a normal amplitude of positive motor fusion.

5. What are realistic long-term treatment outcomes?

The high rates of recurrence reported in some studies raise the question whether it is possible to 'cure' X(T). It also remains unclear at what point treatment outcomes should be recorded: six months, one year, two years etc. following treatment?

6. What is the role of non-surgical treatment?

It has been variously suggested that surgical outcomes are optimised if combined with non-surgical treatment, that non-surgical treatments may be as effective as surgery with less risk, and that non-surgical treatment is appropriate only in small angle exodevations. The role of non-surgical treatment and the effectiveness of different types of non-surgical treatment are unclear.

7. Is early surgery better than late surgery?

The controversy regarding the optimum age for surgery remains unresolved. The risks associated with early surgery are overcorrection leading to loss of stereoacuity and the development of amblyopia, but the benefits are that successful surgery may be more likely to restore normal binocular alignment. It may be that age at onset or the duration affect the outcome more than age at surgery, or it may be that each of these does not greatly affect outcome. As yet these issues remain unanswered.

8. Is unilateral surgery or bilateral surgery more effective?

It has been suggested that simulated distance exotropia and basic X(T) should be treated with a unilateral recess resection, and that true distance exotropia should be treated with bilateral lateral rectus recessions. Only one clinical trial (Kushner 1998a) has addressed this issue, and only for the basic type of X(T).

9. Is initial postoperative overcorrection advantageous?

Retrospective studies are divided on whether or not an initial postoperative overcorrection is advantageous. It may be that initial overcorrection plays a role in lasting binocular stability, or initial overcorrection may simply delay inevitable postoperative drift and recurrence of X(T).

10. What is the optimal treatment for small angle X(T)?

Non-surgical treatment has been advocated, as has a single lateral rectus recession. What constitutes a 'small' angle and whether or not and how it should be treated remain unclear.

11. What are the effects of X(T) on health-related quality of life?

These potential effects are not well described. Such data may be important for guiding the management of the condition and for more clearly defining the benefits versus the risks of surgery.

Quality of the evidence

The overall methodological quality of the included trial was good. However, although most of the domains were assessed as low risk of bias the author did not perform masked assessment of the outcome. The outcomes were assessed by the surgeon who performed surgery, which might lead to potential biases. This weakens the credibility of the results. In addition, as mentioned above, the evidence can only be applied to a specific subgroup of X(T) and its applicability to other subgroups of X(T) remains unclear.

Across all identified studies, measures of severity and thus criteria for intervention are poorly validated, and there appear to be no reliable natural history data. There is, therefore, a pressing need for improved measures of severity and a better understanding of the natural history, and carefully planned clinical trials of treatment to improve the evidence base for the management of this condition.

Potential biases in the review process

We are unaware of any potential biases in the review process.

AUTHORS' CONCLUSIONS

Implications for practice

The one randomised study eligible for inclusion in this review found unilateral recess or resect surgery to be more effective than bilateral recession surgery in correcting basic X(T). This provides some guidance for this subgroup of X(T) but generally there remains a significant lack of reliable evidence to help inform practice. In the absence of good evidence of treatment effectiveness, the potential to do harm by correcting the appearance of misalignment but disrupting the ability to maintain BSV should be seriously considered when managing this condition.

Implications for research

There is a clear need for further randomised studies to provide more reliable evidence for the management of this condition. In particular, to:

- establish the natural history of the condition;
- clarify appropriate intervention criteria for non-surgical and surgical treatments;
- improve methods to measure severity;
- identify the most effective surgical procedure for different types of X(T), e.g. simulated and true distance X(T);
- establish realistic treatment aims and long-term outcomes;
- determine influence of age and duration of misalignment on outcome;

- establish the effectiveness of non-surgical treatments;
- identify whether or not initial overcorrection is advantageous in achieving optimal treatment outcomes;
- measure effects of X(T) on quality of life.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Kushner 1998a

Methods	Randomised trial comparing 2 different surgical interventions for basic X(T).
Participants	Children diagnosed with basic X(T): near deviation within 10 dioptres of distance.
Interventions	Bilateral lateral rectus recession or unilateral lateral rectus recession with medial rectus resection.
Outcomes	At a minimum of 1 year post surgery (12 to 15 months): Satisfactory: between 10 dioptres exophoria and 5 dioptres esophoria Unsatisfactory: any manifest deviation or postoperative treatment.
Notes	'Control' group also included in study but not reported here as comprises a different subgroup of X(T) all undergoing same surgical procedure.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The methods used for sequence generation are not described in the manuscript. We contacted the author for further details and clarified that a computer generated random sequence was created.
Allocation concealment (selection bias)	Low risk	It is unclear in the manuscript whether or not there was concealment of treatment allocation. We contacted the author who clarified that the randomisation assignment was put in a series of sequentially numbered sealed envelopes, the contents of which were unknown until after surgery was scheduled and informed consent obtained.
Blinding (performance bias and detection bias) All outcomes	High risk	There was no masking of participants or outcome assessor. Outcomes were assessed by the surgeon who performed surgery.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants (1 from each randomised group) were lost to follow up and were therefore excluded from outcome analysis. All other included participants had complete outcome data.
Selective reporting (reporting bias)	Low risk	99 patients were operated on during the study enrolment period, some of whom were excluded because they were recruited for another study (Kushner 1998b). As it was unclear why or how participants were included in this study rather than the other study, and at what point participants were randomised, we contacted the author for further information: 29 patients were excluded from Kushner 1998a because, according to a predetermined protocol, if they were eligible for the other study (Kushner 1998b) they were automatically selected for recruitment to it. We determined that this did not constitute selective reporting.
Other bias	Low risk	Final outcomes were measured 'at least one year' following surgery and varied from 12 to 15 months across the entire study population. Further to communication with the author, we clarified that the follow up was 12 to 15 months for each randomised group. Patients selected for recruitment to this study were those who did not fulfil inclusion criteria for another randomised study running concurrently (Kushner 1998b). Therefore the group who were eligible for inclusion in Kushner 1998a

Kushner 1998a *(Continued)*

	were those whose exodeviation did not increase after patching or while looking outdoors, representing a subset of the entire basic X(T) population. This is not spelled out in the manuscript but has more implications for the generalisability of the results and is not likely to bias conclusions regarding treatment effect.

X(T): intermittent exotropia

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Broniarczyk-loba	Prospective study comparing two surgical techniques but non-randomised allocation*.
Collur 1998	Conference abstract, and not for intermittent exotropia.
Kushner 1998b	Randomised controlled trial comparing surgery for the basic distance angle or the maximum distance angle elicited post occlusion: this comparison was not relevant to this review.
Lui 1999	Observational study*.
Martin 1989	Non-comparative study looking at the effect of lateral incommitance on intermittent exotropia outcomes.
Rajavi 2001	Conference abstract, and not for intermittent exotropia.
Zeng 2005	Non-randomised study*.

* studies requiring translation

Characteristics of studies awaiting assessment *[ordered by study ID]*

ISRCTN04267774

Methods	This is a feasibility study of a multi-centre randomised controlled trial of early versus late surgery for intermittent distance exotropia.
Participants	Patients diagnosed with intermittent distance exotropia
Interventions	Early versus late surgery for intermittent distance exotropia
Outcomes	Not provided at time of registration
Notes	This study lacked a majority of key information when registered. It was conducted from 09/01/2002 to 08/31/2003, but there was no publication for the study.

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12610001053011

Trial name or title	Surgery for intermittent Exotropia: A Comparison of Outcomes Following Two Different Surgical Techniques

ACTRN12610001053011 *(Continued)*

Methods	Patients have intermittent exotropia who need surgical intervention and have been referred to the eye clinic by ophthalmologist or orthoptist will be randomised to treatment and allocation is concealed via computer. The randomisation will be done via computerised sequence generation. Group one will have bilateral (both right and left eye) lateral rectus recession. Group two will have lateral rectus recession and medial rectus resection on the same eye.
Participants	Inclusion criteria • Age 3-18 years • History of intermittent exotropia, intermittent at either near or distance • Full eye movements • Visual acuity 6/9 or better each eye, best corrected with crowded test by the time of surgery • Any myopic refractive error, anisometropia or astigmatism of 1 dioptre or greater or hyperopia which is reducing the vision to less than 6/9, must be treated prior to inclusion • Basic exotropia with difference between near and distance measurements <10 dioptres, or simulated divergence excess with difference between near and distance measurement <10 dioptres after +3.00 test and/or patch test • Able to obtain full informed consent from the family for randomisation • Able to obtain accurate prism cover test measurements (distance and near cover test within 5^ on at least 2 visits)
Interventions	Intervention 1: Bilateral lateral recti recession or recession/resection. the recession of the lateral rectus muscle involves weakening the muscle by pulling it back few mm (each mm will weaken the muscle by 3 dioptres) so the amount will depend on the degree of divergent squint. e.g to correct 30 dioptres of divergent squint will need to weaken each lateral recti muscle by 5 mm on each side so in total 10 mm = 30 dioptres. For the medial rectus resection means strengthening the muscle by cutting it (each mm will strengthen the muscle by 4 mm) and that is again dependent on the amount of squint. The duration of each procedure will be approximately 20 min/muscle. Intervention 2: Active control, lateral recti recession procedure is the standard procedure for the intermittent divegernt squint. However some advocate recession/ resection procedure. So the aim is to compare the outcome of both techniques.
Outcomes	Primary outcome: Comparison between two techniques for intermittent exotropia. Bilateral lateral recti reccession or medial/ lateral rectus recession/ resection regarding the success rate and this is measured by dioptre (the surgery considered successful if the residul squint is less than 10 dioptres at 2 years after randomisation). Secondary outcome: To test whether the patch alter the distance measurements and therefore the surgical target the effect of patch test at 2 years after randomisation. We patch the involved eye for 20, 40 ,60 min at different intervals and measure amount of squint in dioptres.
Starting date	1 March 2011
Contact information	Rasha Altaie; Department of ophthalmology The University of Auckland Private Bag 92019 Auckland 1142 New Zealand; Tel: 0064 21220 586; rasha.altaie@gmail.com

ACTRN12610001053011 *(Continued)*

Notes	The study has not yet recruited any participants.

ISRCTN44114892

Trial name or title	An External Pilot Study to Test the Feasibility of a Randomised Controlled Trial comparing Eye Muscle Surgery against Active Monitoring for Childhood Intermittent Distance Exotropia (X(T))
Methods	Patients are randomised to receive either eye muscle surgery or active monitoring for childhood intermittent distance exotropia (X(T)).
Participants	Inclusion criteria: 1. Age ≥ 6 months and ≤ 16 years 2. Diagnosis of intermittent exotropia on the basis of parental history and clinical examination within 6 months of recruitment 3. Newcastle Control Score = 3 4. Minimum size of squint of 15 prism dioptres 5. If aged 4 years and over evidence of near stereopsis i.e. ability to use the eyes together Target gender: male and female; Upper age limit 16 years; Lower age limit 6 months Exclusion criteria: 1. Age under 6 months or over 16 years 2. Previous treatment for intermittent exotropia 3. Constant exotropia = 10 prism dioptres 4. Constant exotropia < 10 prism dioptres with absent near stereopsis 5. Intermittent exotropia where near misalignment is = 10 prism dioptres more than the distance misalignment (convergence insufficiency) 6. Amblyopia (poor vision) > 0.5 LogMAR in either eye 7. Structural ocular pathology 8. Significant neurodevelopmental delay 9. Families requiring translation services
Interventions	Surgery, eye muscle surgery
Outcomes	Primary outcomes: number of patients; Timepoint(s): to determine whether participating centres are likely to recruit a sufficient number of patients. Secondary outcomes: 1. Pilot procedures; Timepoint(s): to pilot procedures involved in the trial including recruitment, randomisation, surgery and masking. 2. Questionnaires; Timepoint(s): to identify through questionnaires reasons why parents decline permission to participate. 3. Recruited patients; Timepoint(s): to determine whether recruited patients remain in allocated groups.

ISRCTN44114892 *(Continued)*

Starting date	01/09/2011
Contact information	Mr MP Clarke: m.p.clarke@newcastle.ac.uk
Notes	This is an ongoing study conducted in the United Kingdom.

IXT1 2012

Trial name or title	Bilateral Lateral Rectus Recession Versus Unilateral Recess-Resect for Intermittent Exotropia (IXT1)
Methods	Participants are randomised to receive either bilateral lateral rectus recession (BLRrec) or unilateral lateral rectus recession with medial rectus resection (R&R).
Participants	Inclusion criteria: • Age 3 to < 11 years • Intermittent exotropia (manifest deviation) meeting all of the following: 1. Intermittent exotropia at distance or constant exotropia at distance and either intermittent exotropia or exophoria at near 2. Largest exodeviation at either distance, near or remote distance between 15 and 50 PD (inclusive) by prism and alternate cover test (PACT) 3. Exodeviation at least 15 PD at distance and near by PACT 4. Basic type or pseudo divergence excess type • Stereoacuity of 400 arcsec or better at near by Preschool Randot stereotest (better of 2 measures) • Visual acuity in the worse eye at least 0.3 logMAR (20/40 on ATS HOTV or 70 letters on E-ETDRS) • No interocular difference of visual acuity more than 0.2 logMAR (2 lines on ATS HOTV or 10 letters on E-ETDRS testing) • Absence of high AC/A ratio (exclude > 6:1) • No previous intraocular surgery, strabismus surgery, or botulinum toxin treatment • Investigator planning to perform surgery for correction of IXT • No hyperopia greater than +3.50 D spherical equivalent (SE) in either eye Exclusion criteria: • Co-existing vertical deviation, oblique muscle dysfunction, DVD, or A or V pattern, any of which the investigator plans to address with vertical transposition of horizontal rectus muscles, oblique surgery, or vertical rectus muscle surgery, i.e. only small vertical deviations, oblique muscle dysfunction, DVD, and A or V patterns not requiring surgery are allowed • Limitation of ocular rotations due to restrictive or paretic strabismus • Craniofacial malformations affecting the orbits • Interocular visual acuity difference of more than 0.2 logMAR (2 lines on ATS HOTV for patients 3 to < 7 years old or 10 letters on E-ETDRS for patients ≥ 7 years old) and/or investigator plans to initiate amblyopia treatment at this time • High AC/A ratio (exclude > 6:1 by gradient method) • Prior strabismus surgery or botulinum toxin injection • Ocular disorders that would reduce visual acuity (except refractive error) • Prior intraocular or refractive surgery • Significant neurological impairment such as cerebral palsy. Patients with mild speech and/or learning disabilities are eligible • Investigator planning to change refractive correction at this time (if the patient is otherwise eligible, the investigator should consider prescribing refractive correction and bringing the patient back at a later time for enrollment)
Interventions	Intervention 1: Active comparator: bilateral lateral rectus recession

IXT1 2012 *(Continued)*

	Bilateral lateral rectus recession (BLRrec) Bilateral lateral rectus recession surgery Intervention 2: Active comparator: unilateral lateral rectus recession with medial rectus resection Unilateral lateral rectus recession with medial rectus resection (R&R) A unilateral lateral rectus recession combined with a medial rectus resection in the same eye. Choice of eye at investigator discretion based on any interocular difference, position under anesthesia, fixation preference, or forced duction testing. Reason for choice of eye will be recorded. Other name: R&R
Outcomes	Primary outcome measures: surgical failure as assessed by motor alignment and stereoacuity at near (Time frame: 3 years) (Designated as safety issue: No) Secondary outcome measures: distance stereoacuity (Time frame: every 6 months for 3 years of follow up) (Designated as safety issue: No) monofixation status (Time frame: every 6 months for 3 years of follow up) (Designated as safety issue: No) development of amblyopia (Time frame: every 6 months for 3 years of follow up) (Designated as safety issue: No) health-related quality of life (Time frame: every 6 months for 3 years of follow up) (Designated as safety issue: No)
Starting date	December 11, 2009
Contact information	Danielle L Chandler, M.S.P.H. 813-975-8690 pedig@jaeb.org
Notes	The study is a multi-centre trial conducted in the United States of America, and is currently recruiting participants.

IXT2 2012

Trial name or title	Observation Versus Occlusion Therapy for Intermittent Exotropia (IXT2)
Methods	Patients are randomised to either the occlusion treatment group which they will receive occlusion (patching) for 3 hours per day for at least 3 months or the no intervention (observation) group.
Participants	Inclusion criteria: • Age 12 months to < 11 years • Intermittent exotropia (manifest deviation) meeting all of the following criteria: 1. intermittent exotropia at distance OR constant exotropia at distance and either intermittent exotropia or exophoria at near 2. exodeviation at least 15PD at distance OR near measured by prism and alternate cover test (PACT) 3. exodeviation at least 10PD at distance measured by PACT • No previous surgical or non-surgical treatment for IXT (other than refractive correction) • Visual acuity in the worse eye at least 0.3 logMAR (20/40 on ATS HOTV or 70 letters on E-ETDRS) for children ≥ 3 years of age • No interocular difference of visual acuity more than 0.2 logMAR (2 lines on ATS HOTV or 10 letters on E-ETDRS) for children ≥ 3 years of age • No hyperopia greater than +3.50 D spherical equivalent in either eye • No myopia greater than -6.00 D spherical equivalent in either eye • No prior strabismus, intraocular, or refractive surgery • No abnormality of the cornea, lens, or central retina

IXT2 2012 *(Continued)*

	• Investigator willing to observe the IXT untreated for 3 years unless specific criteria for deterioration are met Exclusion criteria: • Pure phoria at both distance and near • Prior non-surgical treatment for IXT other than refractive correction (e.g. vergence therapy, occlusion, vision therapy/orthoptics, or deliberate over-minus with spectacles more than 0.50D) • Previous amblyopia treatment other than refractive correction within 1 year • Vision therapy/orthoptics for any reason within the last year • Interocular visual acuity difference more than 0.2 logMAR (2 lines on ATS HOTV for patients 3 to < 7 years old or 10 letters on E-ETDRS for patients ≥ 7 years old) (patients ≥ 3 years only) and/or investigator plans to initiate amblyopia treatment at this time. • Limitation of ocular rotations due to restrictive or paretic strabismus • Craniofacial malformations affecting the orbits • Ocular disorders which would reduce visual acuity (except refractive error) • Prior strabismus surgery or botulinum injection, intraocular surgery, or refractive surgery • Strabismus surgery planned • Known skin reactions to patch or bandage adhesives • Significant neurological impairment such as cerebral palsy. Patients with mild speech delays or common reading and/or learning disabilities are not excluded. • Investigator planning to change refractive correction at this time (if the patient is otherwise eligible, the investigator should consider prescribing refractive correction and bringing the patient back at a later time for enrollment)
Interventions	Intervention 1: No intervention (Observation); patients randomised to the observation group will receive no treatment (other than refractive correction). Intervention 2: Active comparator, occlusion therapy; Device: occlusion treatment; Patients randomised to the occlusion treatment group will receive occlusion (patching) for 3 hours per day for at least 3 months. Choice of which eye to occlude, or whether to alternate daily, is at investigator's discretion. Other names: occlusion, therapy occlusion, treatment patching.
Outcomes	Primary outcome measures: deterioration by 6 months as assessed by motor alignment and stereoacuity at near (Time frame: 6 months) (Designated as safety issue: No) Deterioration by 3 years as assessed by motor alignment and stereoacuity at near (Time frame: 3 years) (Designated as safety issue: No) Secondary outcome measures: distance stereoacuity (Time frame: every 6 months for 3 years of follow up) (Designated as safety issue: No) monofixation status (Time frame: every 6 months for 3 years of follow up) (Designated as safety issue: No) development of amblyopia (Time frame: every 6 months for 3 years of follow up) (Designated as safety issue: No) health-related quality of life (Time frame: every 6 months for 3 years of follow up) (Designated as safety issue: No)
Starting date	January 2010
Contact information	Danielle L Chandler, M.S.P.H. 813-975-8690 pedig@jaeb.org
Notes	The study is a multi-centre trial conducted in the United States of America, and is currently recruiting participants.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Exotropia] explode all trees
#2 MeSH descriptor: [Strabismus] this term only
#3 Divergen* and (excess* or strabismus)
#4 Exotrop* or IDEX
#5 Intermitten* and exotrop*
#6 Ocular* near/10 (misalignment or deviat*)
#7 #1 or #2 or #3 or #4 or #5 or #6

Appendix 2. MEDLINE (OvidSP) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. strabismus/
14. exotropia/
15. ((excess$ or strabism$) adj10 diverge$).tw.
16. (exotrop$ or IDEX).tw.
17. (intermitt$ adj10 exotrop$).tw.
18. ((misalig$ or deviat$) adj10 ocular$).tw.
19. or/13-18
20. 12 and 19

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville (Glanville 2006).

Appendix 3. EMBASE (OvidSP) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/

26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. intermittent strabismus/
34. divergent strabismus/
35. ((excess$ or strabism$) adj10 diverge$).tw.
36. (exotrop$ or IDEX).tw.
37. (intermitt$ adj10 exotrop$).tw.
38. ((misalig$ or deviat$) adj10 ocular$).tw.
39. or/33-38
40. 32 and 39

Appendix 4. LILACS search strategy

intermitt$ and exotrop$

Appendix 5. *meta*Register of Controlled Trials search strategy

exotropia

Appendix 6. ClinicalTrials.gov search strategy

Exotropia

Appendix 7. ICTRP search strategy

exotropia

WHAT'S NEW

Date	Event	Description
8 April 2013	New citation required but conclusions have not changed	Issue 5 2013: Three ongoing studies and one study awaiting assessment added.
24 January 2013	New search has been performed	Issue 5 2013: The electronic searches were updated.

HISTORY

Protocol first published: Issue 3, 2002
Review first published: Issue 2, 2003

Date	Event	Description
30 January 2009	New search has been performed	Issue 2, 2009: updated search yielded no new trials. The background section has been updated.
16 May 2008	Amended	Converted to new review format.
24 May 2006	New search has been performed	The updated version of this review includes a broader spectrum of intermittent exotropia: initially we restricted inclusion to studies specifying intermittent distance exotropia. However in many cases distance and basic types of intermittent exotropia are not differentiated from each other and are pooled together. This is

Date	Event	Description
		consistent with clinical observations which often show an individual to change from distance to basic from visit to visit. In light of the amended inclusion criteria, one study previously excluded, now qualifies for inclusion.
24 May 2006	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

Sarah Hatt and Lawrence Gnanaraj were both responsible for the original review:
Designing the review
Data collection for the review
Screening search results
Screening retrieved papers against inclusion criteria
Appraising quality of papers
Abstracting data from papers
Writing to authors of papers for additional information
Obtaining and screening data on unpublished studies
Data management for the review
Entering data into RevMan
Analysis of data
Interpretation of data
Writing the review

Xue Wang was responsible for assisting Sarah Hatt in the most recent update of the review, providing help with:
Screening search results
Screening retrieved papers against inclusion criteria
Abstracting data from papers
Entering data into RevMan

Sarah Hatt was also responsible for co-ordinating the review.

DECLARATIONS OF INTEREST

None known

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Internal sources

- No sources of support supplied

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- National Eye Institute, National Institutes of Health, USA.

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INDEX TERMS

Medical Subject Headings (MeSH)

Exotropia [*surgery] [therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans